Environmental Health Perspectives
Vol. 60, pp. 233-239, 1985

Potential Reproductive and Postnatal Morbidity from Exposure to Polychlorinated Biphenyls: Epidemiologic Considerations

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There is both laboratory and epidemiologic evidence that PCBs are toxic to several phases of reproduction. Workplace exposure is an important but small part of the exposure to these compounds, since most of the population has detectable levels in blood or fat. Studies in the general population on PCBs and reproduction have not been done. Some studies in workers are under way, and in epidemic PCB poisonings, small babies with a distinct clinical syndrome are seen. We review some of the laboratory and epidemiologic data and the methods available for study of reproduction in humans; study of any highly exposed group should be done and studies of spontaneous abortion, birth weight and certain congenital anomalies should look for an effect of PCBs.

Introduction

Successful human reproduction is a complex cycle that can be broken arbitrarily into stages: conception, the carriage of the fetus to term, the birth of a normal baby, post-natal nurturance, and normal growth and development. This cycle is closed with its reiteration by the offspring. We regard interference with any of these processes as a morbid event, even when clinical illness is not apparent. There is evidence both from outbreaks of human illness and from laboratory experiments that polychlorinated biphenyls (PCBs) or chemical compounds very similar to them can disrupt most of the phases of reproduction; whether they do so at the levels of exposure commonly encountered in the general population or in the workplace is not known.

We consider here the available epidemiologic data relating PCBs to reproduction. We also consider some of the epidemiologic methods for study of reproductive morbidity. Since the emphasis here is on a particular exposure, the "natural" methods of study are of populations who are surveyed for exposure and illness, or of cohorts whose exposure is documented and who are followed to see what illnesses they develop. However, much of what is known about the toxicity of PCBs has come from the study of epidemics, in which sick people were investigated and found to have been poisoned. Thus we will discuss the case-control approach where it seems useful. Details of study feasibility and the large experimental literature on PCBs are beyond the scope of this paper, but a few comments arise on both. We note first, though, the difficult problem of studying a group of chemicals that have become sufficiently widespread in the enviroment that population exposure, in the sense of detectable residues in body tissues, is almost universal.

Use, Spread, and Human Exposure

Over 800 million tons of PCBs were produced and distributed worldwide from their introduction in the 1930s until restrictive regulations in the 1970s (*1*). Besides closed applications in heavy transformers, PCBs were also the oily pigment suspension agent in carbonless copy paper, were part of microscope immersion oil, were in ballasts and capacitors in consumer electrical goods, and were a vehicle for application of pesticides. Exposure of workers to PCBs represents a small, albeit important, part of the human exposure to these compounds. More widespread exposure has resulted from the dispersion or disposal of these goods in ways, such as recycling carbonless copy paper, that were not recognized as unsuitable or hazardous. PCBs are very stable; they resist both physical degradation by agents in the environment and metabolic degradation by organisms.

Like DDT (*2*), PCBs bioconcentrate. Environmental levels in water are quite low; single-celled organisms will come into a steady state with them. However,

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predators store essentially all that they ingest over a lifetime, and thus all organisms other than primary consumers encounter levels above ambient ones. An ecologic rule of thumb is that concentrations increase about one order of magnitude per link up the food chain. Hence, fish-eating birds will have tissue levels thousands of times higher than the sediment levels in the water where they prey. Man lives quite high on the food chain, and there is monitoring data available to show that PCBs are detectable at high prevalence in unselected groups of people (*3–5*). This is likely to be due to low level contamination of the food supply, particularly of predators like big fish (*6*).

Human vulnerability to contaminated food comes not only from our position on the food chain, but also from the complexity of the systems used to grow and distribute foodstuffs. Accidental contamination of food from wrappers made from recycled paper (*7*) and of meat and dairy products contaminated from leaking machinery (*8*) have occurred in the past. Most notable are the two major outbreaks of Yusho, which were both caused by contaminated oil from leaking heat process machinery (*9*). Even organic gardeners are at risk; an incident in Bloomington, Indiana, involved the use of sewage sludge contaminated with PCBs as organic material incorporated into garden soil (*10*). The sole remaining dietary source that is regularly heavily contaminated is sport fish caught from polluted waters. However, continued human exposure from other sources is certain. This is due to the large amounts of PCBs in use, the gradual turnover and disposal of machinery and other goods containing them, and the difficulties encountered in hazardous waste handling in general.

Besides dietary exposure, there are at least two other routes by which people could be appreciably exposed. Because of the oily, adherent nature of PCBs, they could be carried home on soiled workclothes. Although there is not a clear example of this having happened for PCBs, work clothes soiled with dioxin and brought home have produced chloracne in the children of workers (*11*); this vector is thus capable of producing biologically active exposure, and good industrial hygiene practices are warranted. Since PCBs are dermally absorbed, reproductively active workers or workers with children should be aware of this route. Improper waste disposal can produce direct exposure; in North Carolina, 200 miles of roadside were contaminated by dumped PCBs resembling Aroclor 1260, a heavily chlorinated mixture. Women who lived on the road or crossed it regularly had heavier congeners in their milk more frequently than controls (*12*). Overall levels were no higher and no illnesses have been reported.

It is thus difficult to speak of "exposed" and "unexposed" groups of people. Occupational exposure and the exposure of heavy consumers of sport fish are probably the highest, but these may well overlap with exposure from accidents involving waste disposal or food contamination. Thus any occupational study must deal with the background of exposure that is usually present. On the other hand, studies of general effects on populations must confront ubiquitous, low level exposures.

In addition, the congeneric composition of PCB mixtures will differ, as will the amount of contamination by terphenyls, quatraphenyls and furans, depending on the original source, the kind of use and the degree of degradation. For example, the two outbreaks of Yusho involved mixtures heavily contaminated with these other chemicals, so it is not clear to what extent the results observed there apply to other situations.

Pharmacology and Dose

PCBs are strongly lipophilic, and many of the congeners are refractory to either metabolic breakdown or the attachment of a moiety that would make them water soluble. Since healthy human beings excrete virtually no fat (except when lactating), the compounds accumulate in fatty tissue. There are few data on absorption, distribution, and excretion of PCBs in man; in general, though, it is reasonable to assume that there are few barriers to diffusion, that the compounds will dissolve in any fat, and they will thus be present in a given organ or tissue in proportion to its fat content. These assumptions lead to a simple pharmacokinetic model: PCBs are absorbed from the gastrointestinal tract or through the skin, dissolve in the fat of serum, and come to steady state with fat in tissues. Thus, fatty and nerve tissue should be highest, most visceral organs intermediate, muscle and bone lowest. Blood has a variable amount of complex fat; the amount of PCB found in a serum sample at a given time will depend on both "body burden" and serum fat. Since excretion is very slow or absent, a cessation of externally administered dose does not lead to lowered blood levels; the PCBs in serum fat stay in steady state with stores in body fat. Large weight losses should decrease the size of the compartment but not the amount of PCBs, thus levels should go up. During lactation, fats are secreted but weight does not change much; levels should go down.

There have been many investigations of PCBs in blood, fatty tissue, or milk. In general, measurable levels are ubiquitous, with the prevalence of positive samples dependent on the sensitivity of the method used; levels are highest among workers and consumers of polluted sport fish (*3*). In some studies, blacks are higher than whites (*13*), males higher than females, and older people higher than younger (*4*). For simple calibration purposes, consider a 25 year old lactating woman weighing 60 kg. We expect a PCB concentration of 1.8 ppm in the fact of her milk; this is the median in the 850 women in our North Carolina study of the effects of PCBs on nursing children. If she is 20% fat, she has about 22 mg total body burden. She presumably got this from background food contamination; spread uniformly over her lifetime, this is 2.4 μg/day. At her current weight, this represents 0.04 μg/kg/day. If her milk is 2% fat, she will have 36 ppb in whole milk. At

0.5% fat, she will have about 9 ppb in serum; this is the median in our data. Serum levels in the general population range up to 60 ppb (*3,4*). Studies of workers have found means of 33 ppb (*14*), 37 ppb (*15*), 75 ppb (*10*) and 150–300 ppb (*16*).

To put this into toxicological perspective, the most sensitive biologic phenomena thus far reported involves the induction of microsomal enzymes of the P450 class (*17*), or the covalent binding to macromolecules in microsomes (an intermediate step in enzyme induction) (*18*). Both occur in a dose related fashion beginning at about 1 to 4 μg/kg/day. Decreased fertility and small offspring were seen in experiments in which rhesus monkeys were fed 2.5 ppm PCBs in the diet (about 100 μg/kg/day). These monkeys had 33 ppm PCBs in their adipose tissue near conception, and their milk later had 275 ppb or 16 ppm fat basis (*19,20*). Most other experiments have been carried out at substantially higher doses.

Placenta has very little fat, and in our data not much PCB is detectable there. PCBs do cross the placenta, and there are cases of congenital PCB poisoning (*21*). Cord blood, however, is lower than term maternal blood (*22*); this is due at least in part to the three-fold difference in fat content.

The 5 kg infant of the hypothetical woman above drinks 800 mL per day of milk; he gets 29 μg/day, or about 6 μg/kg/day. This is substantially above any "safe" level calculated for regulatory or advisory purposes; the Allowable Daily Intake for PCBs as set by the Food and Agriculture Organization is 1 μg/kg/day (*23*). Given the available toxicity data, the possibility of toxicity occurring in breast fed children can not be ruled out on a dose basis alone. However, in general, breast-fed infants thrive, and there are thus far no case reports of illness in a breast fed child attributed to PCBs at population levels. There has not been an organized study of levels in breast milk in PCB workers. There are, however, Japanese data that show that women who work around PCBs have higher levels in their milk, that their nurslings absorb and store the chemicals, and that levels in children's sera are proportional to the duration of breast feeding (*15*). In the Japanese Yusho epidemic, Harada reports cases produced by breast milk exposure alone (*24*), and there is suspicion of such cases in Taiwan. Few samples of milk have been analyzed from either outbreak; of those in the literature, the values found are about the same as those in the Japanese population (*25*).

Study of Human Reproduction

It is established that human beings are exposed to PCBs, and that the compounds can disturb reproductive function. It is often difficult to show that such dysfunction as occurs in a given group of people is attributable to PCB or any other exposure, however. We will consider here the various reproductive outcomes that are studied epidemiologically, some of the ways in which they are studied, data on human studies of PCBs when available, and relevant laboratory data.

Fertility

There have been no formal studies of fertility dysfunction among humans exposed to PCBs. The suspicion that the compounds are potentially active on human fertility comes from experiments done on rhesus monkeys, where a total diet containing 2.5 ppm PCBs led to prolonged time to conception and fetal wastage (*19*). The same study showed no changed in semen characteristics of the male, or in the males' capacity to reproduce.

Interest in the study of environmental effects on human fertility is relatively recent. Furthermore, epidemiologic tools for measuring such effects have not yet been well developed. Major effects of chemicals on fertility have been detected more often by the affected persons themselves than by epidemiologic research (*26,27*).

Epidemiologic studies of fertility can compare vital statistics data from population groups as a whole, or can compare groups using data obtained from individual persons. Each approach has limitation.

The advantage of the vital statistics approach is that birth certificate and census data are easily accessible. By combining them one can calculate birth rates for geographic areas such as states or countries. Although one could link such data with population exposure information, the birth rate by itself is probably not very sensitive to environmental factors. Other influences, particularly contraceptive usage and desired family size, probably overshadow the relatively small differences attributable to lowdose environmental exposures to substances such as PCBs. In specific settings where variation in PCB exposure is higher but where small numbers of people are involved, the live birth rate is unstable (that is, subject to wide chance fluctuations).

When individuals are available for study, more specific comparisons can be made of the rates of occurrence of clinical infertility, or of the average time taken to achieve pregnancy, live birth, or desired family size. Contraceptive practices and other factors known to affect the chance of conception can be accounted for in design and analysis. This general approach has promise for the detection of more subtle effects on fertility, such as might be expected from the low levels of PCB exposure commonly seen. A few strategies of this kind have been proposed (*28,29*), but none is yet well worked out.

Semen analysis is ordinarily not performed unless there is evidence of fertility impairment. The use of semen analysis in the study of environmental effects is complicated by the fact that sperm can vary widely in their characteristics without affecting fertility. Recent development of sperm penetration assays, e.g., Karp, (*30*) may refine the ability to detect toxic effects on semen.

Spontaneous Abortion

There are several cohorts of persons under observation who have been exposed to relatively high doses of PCBs: capacitor factory workers in upstate New York (*31*), insulation workers in Japan (*22*), and both Japanese (*32*) and Taiwanese (*33*) families exposed to PCB-contaminated heat exchange fluid in their cooking oil. Thus far, none of these studies has shown a convincing effect of PCBs on rates of spontaneous abortion. However, the numbers of persons in these cohorts is not large (all less than 2000), and as a consequence their statistical power to show an effect is low.

Rhesus monkeys exposed to PCBs in concrete sealant in their cages (*34*) or experimentally given PCBs at 2.5 and 5 ppm in the diet (*19*) had increased spontaneous abortions and stillbirths. In both instances, however, the female monkey had alopecia, erythema and edema of the eyelids, and nonspecific metabolic abnormalities. Thus, although it is clear that exposure to PCBs can produce pregnancy loss, it is not clear that they will do so at low doses not clinically toxic to the mother.

Spontaneous abortion among humans occurs in perhaps 15% to 20% of recognized pregnancies. Even though such loss is common, it is not easy to measure epidemiologically. The occurrence of abortion can be measured in one of two general ways. One is to collect data on abortions that have occurred some time in the past (retrospective data). The other is to collect data on abortions at the time they occur (prospective data). By using retrospective data, one can study much larger numbers of abortions for a given population; however, the quality of those data is poorer.

Retrospective spontaneous abortion data come from either clinical records or personal interviews. Clinical records are incomplete in that not every woman who has a spontaneous abortion sees a doctor, or needs to. For those women who do receive medical attention, the event may be recorded in hospital records or clinic records or private physicians' files in such a way that it is not easily retrieved. This is especially true in the US, where medical records are seldom usable as a primary data source in the study of spontaneous abortion.

An alternative strategy for collecting retrospective data is to interview the women themselves. Women's recall of previous abortions is incomplete (*35*); furthermore, recall may be biased if women are alarmed about their exposure to a potential toxin. The quality of such abortion data can sometimes be improved by using medical records to verify reported abortions. Recall bias may be reduced in this way, and additional information about the pregnancy may be obtained. This approach has been used in studies of spontaneous abortion among women who lived in areas sprayed with 2,4,5-T and around the Love Canal (*36*). In general, this retrospective approach may be the most suitable for exploring possible pregnancy loss among PCB-exposed women.

Prospective studies of any exposed group are possible but difficult, given the relative infrequency of pregnancy. Currently in the US there are about seven births per year per 1000 women aged 15 to 44. The number of observable pregnancies expected in a particular exposed group would probably be so small as to make the power of those observations limited.

Case-control studies of spontaneous abortion offer a means of collecting data on a large number of abortions at the time they occur. However, linking those abortions to exposure data is not easy. Unless the study population is unusual, reported exposures to most environmental agents will be rare. This method has worked for furthering understanding of common exposures such as cigarettes, alcohol, and a few drugs, but its usefulness is presumably less for the study of PCBs, for which low exposures are ubiquitous and high exposures are rare.

Fetal loss later in pregnancy is far less common than spontaneous abortion but more accurately documented. Most countries require pregnancy loss that occurs after 20 or 28 weeks of gestation to be registered as stillbirths. Thus, studies of vital records comparing differences in late fetal loss between exposed and unexposed groups are possible. However, the limitations of uncontrolled confounders and unstable rates due to small numbers make this an impractical approach under most circumstances.

Birth Weight

In both of the recorded outbreaks of Yusho, babies born to affected mothers were small for their gestational age (*21*). Studies to low-level exposure to PCBs on birth weight have been less definite than the observations of Yusho mothers. One study reported higher levels of PCBs in the mothers of smaller babies compared to the mothers of larger babies (*37*). However, this is not consistently found. Among laboratory animals, rhesus monkeys exposed to PCBs accidentally (*34*) or experimentally (*19,20*) have been observed to produce small offspring.

Birth weight has several attractive features as an endpoint in the study of environmental exposures. Birth weight differs somewhat from the outcomes previously discussed, in that it is a characteristic of all babies rather than an unusual outcome to be tallied. It is easy to measure, it is required on birth certificates in most countries, it is plausibly an indicator of intrauterine growth, and for the individual infant it is the single strongest predictor of neonatal morbidity and mortality.

Birth weight is usually analyzed by comparing the mean weights of exposed and unexposed groups, or by comparing the occurrence of low birth weight (less than 2500 grams) among groups. While such differences in birth weight may be simple to establish, their interpretation is not straightforward. The relation of birth weight to mortality is such that a difference in mean birth weight or low birth weight between groups does not necessarily mean the groups differ in mortality (*38*).

Teratology

Commercial PCBs that have been in heat exchange service are human teratogens (*21,39*). Affected babies have been seen in the two Yusho outbreaks. Mothers ingested cooking oil contaminated by the PCB mixture; in most cases, mothers of affected babies were themselves obviously ill, and thus little detective work was required. The full-blown syndrome is a small baby with pigmented skin, conjunctivitis, pigmented gums, hypoplastic nails, metastatic scalp calcification, natal teeth, comedones, and hyperbilirubinemia. Thus far, the syndrome has not been reported outside of the two epidemics.

There are a variety of ways in which human teratogens have been studied. Typically, the notion that some agent is teratogenic comes from a clinician, or sometimes a patient, who notices a cluster of some unusual phenotype. Generally, specific congenital anomalies or recognized syndromes of anomalies are rare events; Down's syndrome, the commonest chromosomal anomaly and one of the more common syndromes recognizable at birth, occurs in only 1/600 live births. There is a great variety of anomalies, though, and the aggregate rate of babies born with one is about 3–5%, counting conditions like cystic fibrosis that were known to be present at birth but diagnosed later. Because of the rarity of individual conditions, the case-control approach seems tailor-made, yet it is not that much harder to survey for many other kinds of cases while waiting for the ones of interest to be born. Examples of currently used study designs are as follows.

Registry/Cohort. Patients with some specific illness,like diabetes mellitus (*40*), who are followed medically anyway or people with exposures of interest under routine surveillance (like occupational cohorts) can be followed for pregnancy outcome and any birth defects noted. The attraction to this is that structural anomalies are often very apparent at birth and easy to diagnose and count. However, persuasive studies of birth defects usually require either a very strong effect or very large size. Most cohorts of workers are relatively small and are not regularly producing malformed children at a high rate; thus, the probability of detecting a teratogenic exposure is small. The cohort method has worked best in cases where the mothers themselves were ill, as in Japan. Once the causal nature of the association was clear, the occasional baby born with congenital Yusho but with an unaffected mother could be recognized. One's wish for the etiologic clarity of epidemic situations is tempered by the fact that they are typically public health disasters; however, when they do occur, oportunities for study should be exploited.

Surveillance. The US Centers for Disease Control count all birth defects occurring in Atlanta that are diagnosed by the time the child leaves the hospital. Some information on the medical aspects of the pregnancy is also gathered. This program also surveys birth defects as noted on discharge summaries in about 1/3 of U. S. births. This system has proved useful for expeditious confirmation or denial of hypotheses advanced from other sources, like Poland syndrome and Bendectin (*41*). It is also good for monitoring secular trends, since the problem of partial reporting is "cancelled out" when the same data source is compared with itself over time. Thus far, the system has not proved sensitive to any occupational or specific environmental chemical exposure.

Search for Syndromes. Babies are frequently born with one or more minor anomalies, such as mild midface hypoplasia, hypoplastic nails, or other findings; such children might not be called malformed at all except under careful clinical scrutiny. Workers at the University of Washington assembled such children, looked for recurring clusters of anomalies, and inquired among their parents about unusual exposures. It was in this way that fetal dilantin (*42*) and alcohol (*43,44*) syndromes were described. While the chain of reasoning is somewhat circular, hypotheses about the etiology of such syndromes are readily tested by observing mothers with the suspect exposure prospectively for the specific findings in question. This approach would be unlikely to incriminate a specific occupational exposure if carried out in the general population, but it might be useful to evaluate children in a prepaid clinic or HMO in detail when many of the mothers worked around substances that might be teratogenic.

Case-Control Studies. Studies of obvious individual birth defects or etiologically similar kinds of defects are done, typically when a cluster of some unusual anomaly presents itself. Under the best circumstances, this is an enormously powerful approach, as exploited by McBride for phocomelia and thalidomide (*45*) or Gregg for congenital rubella (*46*). Actually, the designation case-control is a bit too formal for many of these observations, which often consist of a case series with a frequency of some exposure that seems out of line to the investigator.

Lactation

PCBs in breast milk are of interest as an indicator of exposure to the mother and a vector of exposure to the child. In addition, lactation performance is a plausible endpoint for study because of its implications for infant development. In most developed countries, it is standard clinical practice to supplement or wean a child who is ill or is failing to gain weight satisfactorily while breastfeeding. Thus, subtle interference with the nutritional or immunologic activity of breast milk could show up as lactation failure or shortened duration of lactation. This phenomenon has no specific animal model; although dairy cows exposed to polybrominated biphenyls (which differ from PCBs only in the substitution of the halogen) in their feed dried up, this was part of a general clinical syndrome and they were obviously ill (*47*). In our data, women with higher levels of DDE do not breast feed as long; this is not true of women with higher levels of PCB (*48*).

Development

Harada described lethargy and apathy and soft meurological signs in children aged seven to nine who had had Yusho years before (*24*). The growth defect in these children, apparent at birth, was gone by about age four. Formal developmental assessment of these children has not been reported. However, in Michigan farm children exposed to polybrominated biphenyls, scores on a standardized school readiness scale (the McCarthy Scales of Children's Abilities) were lower in children with higher PBB body burden as measured by analysis of fatty tissue (*49,50*). Rhesus monkeys exposed to PCBs experimentally had abnormalities of behavior (hyperactivity at first, hypoactivity at 44 months) and slowed development as measured by speed on learning tasks (*51,52*). We are beginning to accrue data on standard tests of infant behavior, development, and school readiness (the Brazelton Neonatal Behavioral Assessment Scale, the Bayley Scales of Infant Development, and the McCarthy scales) in our project, but analyses of them are not yet available.

Discussion

PCBs or chemicals like them could interfere with any reproductive function discussed above if the dose were to be high enough. The concern about toxicity to reproductive function is that it might occur with no overt signal that toxic levels had been encountered—for example, that an asymptomatic parent might poison a child inadvertently. While no amount of negative data can totally allay such a suspicion, there are certain tactics that appear reasonable, as well as some commonly made suggestions that do not.

One belief or practice that does not bear scrutiny is the emphasis on the reproductively active or pregnant woman as the most sensitive to interference with reproduction. It is biologically plausible to argue that sperm cells, which undergo a more or less continuous process of maturation throughout the male's life, are at least as sensitive as the ovum, embryo or fetus. Thus reproductively active males should share the same concerns about workplace exposures as females. For PCBs specifically, current US guidelines are that PCBs be treated as carcinogens, which for practical purposes means that exposures are limted to the lowest feasible amounts in routine uses and applications. However, nonroutine events, such as leaks and transport, should be expected, so vigilance and prompt action are required.

Various proposals involving testing of biological samples from workers have been made. For example, it has been proposed that female workers have their milk tested, and that those with levels above some specified cutoff be advised not to breast feed. However, given the very high prevalence of detectable background levels, analysis of a sample in the absence of a specific clinical suspicion of illness is rarely warranted. The most likely outcome of such a test is a positive value that is not readily interpretable. No quality control programs exist for analytic procedures for such chemicals, and there is evidence that labs vary substantially within themselves and among each other on duplicate samples (J. Liddle, U.S. Centers for Disease Control, personal communication). There is no body of data that allows clinical interpretation. Analysis is best done in a research setting where results can be evaluated formally. Failing that, it should be made clear in advance that any sample will be likely to show a positive value, and plans for dealing with questions that can be naturally anticipated should be made in advance.

In terms of research, we should exploit opportunities to learn from unusual exposures or potential cases in an epidemic, since this was the way in which much of our current knowledge was gained. Outside epidemics, it seems likely that manifestations of toxicity will be subtle, and only well-organized careful study, innovative reasoning, and detailed clinical and chemical observation will pay off.

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